IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	
Domenico FANARA et al.	:	
Serial No. NEW	:	**Attn: APPLICATION BRANCH**
Filed June 27, 2003	:	Attorney Docket No. 2003_0894

PHARMACEUTICAL COMPOSITIONS FOR THE CONTROLLED RELEASE OF ACTIVE SUBSTANCES
(Rule 1.53(b) Continuation of Serial No. 10/055,962, Filed January 28, 2002)

PRELIMINARY AMENDMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Kindly amend the application as follows:

In parallel, it is increasingly therapeutically advantageous to be able to simultaneously administer by the oral route an active substance released immediately after administration, and the same or a second active substance released gradually and regularly after administration. In the case where the same active substance is simultaneously administered for immediate release and for prolonged release, this makes it possible to rapidly release a sufficient dose of active substance to trigger the desired effect and to maintain this effect by a gradual and prolonged release of the same active substance. In the case where an active substance is released immediately and another active substance is released gradually, this makes it possible to obtain combined therapeutic effects by means of two active substances having very different pharmacokinetic profiles.

In this context, international patent application WO 94/09761 describes a slow release oral composition comprising

a) a matrix core comprising
   - pseudoephedrine sulfate
   - hydroxypropylmethylcellulose
   - ethylcellulose
   - dibasic calcium phosphate
   - povidone
   - silicon dioxide
   - magnesium stearate

and

b) a coating on the matrix core comprising
   - loratadine
   - hydroxypropylmethylcellulose
   - polyethylene glycol 400
   - polyethylene glycol 3350.

European patent application EP-A-0 396 404 describes a slow release oral composition comprising

a) a matrix core comprising
   - ibuprofen
   - pseudoephedrine
   - swellable hydrophilic polymers, such as hydroxypropylmethylcellulose
   - excipient such as dibasic calcium phosphate
   - lubricant such as magnesium stearate,

and

b) a coating on the core comprising

- loratadine
- hydrophilic polymer
- other excipients.

In this context, orally administrable solid pharmaceutical compositions combining, in a single unit, a portion exhibiting immediate release and a portion exhibiting delayed release have been described. However, these compositions require methods of preparation which are technically very sophisticated and/or do not allow the desired release profiles to be obtained for all the active substances.

We have now just discovered, surprisingly, novel pharmaceutical compositions which can be administered orally, allowing the controlled release of pharmaceutically active substances such that a satisfactory therapeutic effect is observed over fairly long periods, for example in only one or even two daily doses.

In particular, the compositions according to the present invention do not require excessive quantities of matrix excipients and allow regular and continuous release of active substances over periods of at least 12 hours.

In addition, we have also just discovered that these new controlled-release pharmaceutical compositions can be used in combination with an immediate-release pharmaceutical composition for the same or for another active substance, in a single unit intended to be administered orally.

The present invention therefore relates to pharmaceutical compositions which can be administered orally, allowing the controlled release of at least one active substance, comprising

a) the said at least one active substance,

b) between 5 and 60% by weight, relative to the total weight of the composition, of at least one excipient, selected from inert matrices, hydrophilic matrices, lipid matrices, mixtures of inert matrices and of lipid matrices, mixtures of hydrophilic matrices and of lipid matrices, mixtures of hydrophilic matrices and of inert matrices, with the exception of mixtures comprising a polyacrylic acid and at least one hydrophilic matrix of the cellulose type;

c) between 5 and 50% by weight, relative to the total weight of the composition, of at least one alkalinizing agent soluble in an aqueous phase under physiological